

**AMENDMENTS TO THE CLAIMS**

This listing of claims will replace all prior versions and listings of claims in the application:

1. **(Withdrawn)** A method of modulating a biological response in a cell, the method comprising contacting the cell with at least one agent that modulates the expression or activity of Err $\alpha$  or Gabp, wherein the biological response is
  - (a) expression of at least one OXPHOS gene;
  - (b) mitochondrial biogenesis;
  - (c) expression of Nuclear Respiratory Factor 1 (NRF-1);
  - (d)  $\beta$ -oxidation of fatty acids;
  - (e) total mitochondrial respiration;
  - (f) uncoupled respiration;
  - (g) mitochondrial DNA replication;
  - (h) expression of mitochondrial enzymes; or
  - (i) skeletal muscle fiber-type switching.
- 2-16. **(Canceled)**
17. **(Withdrawn - Currently Amended)** A method of determining whether if an agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function, the method comprising determining whether if the agent increases:
  - (i) the expression or activity of Err $\alpha$  or Gabp in a cell; or
  - (ii) the formation of a complex between a PGC-1 polypeptide and (i) an Err $\alpha$  polypeptide; or (ii) a Gabp polypeptide;wherein an agent that increases (i) or (ii) is a potential target for the treatment of the disorder.

18. **(Canceled)**

19. **(Withdrawn)** The method of claim 17, wherein the agent increases the formation of the complex, and wherein the agent increases the biological response.

20. **(Withdrawn)** The method of claim 19, wherein the agent decreases the formation of the complex, and wherein the agent decreases the biological response.

21-34. **(Canceled)**

35. **(Withdrawn)** A method of reducing the metabolic rate of a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of an agent which decreases the expression or activity of at least one of the following:

- (i)  $Err\alpha$ ;
- (ii)  $Gabpa$ ;
- (iii) a gene having an  $Err\alpha$  binding site, a  $Gabpa$  binding site, or both; or
- (iv) a transcriptional activator which binds to an  $Err\alpha$  binding site or to a  $Gabpa$  binding site;

thereby reducing the metabolic rate of the patient.

36-41. **(Canceled)**

42. **(Withdrawn - Currently Amended)** A method of identifying a susceptibility locus for a disorder that is characterized by reduced mitochondrial function, glucose intolerance, or insulin intolerance in a subject, the method comprising

- (i) identifying at least one polymorphism ~~polymorphisms~~ in a gene, or linked to a gene, wherein the gene (a) has an  $Err\alpha$  binding site, a  $Gabpa$  binding site, or both; or (b) is  $Err\alpha$ ,  $Gabpa$ , or  $Gabpb$ ;
- (ii) determining whether ~~if~~ at least one polymorphism is associated with the incidence of the disorder,

wherein if a polymorphism is associated with the incidence of the disorder then the gene having the polymorphism, or the gene to which the polymorphism is linked, is a susceptibility locus.

43-46. (Canceled)

47. **(Withdrawn - Currently Amended)** A method of determining whether if a subject is at risk of developing a disorder which is characterized by reduced mitochondrial function, the method comprising determining whether if a gene from the subject contains a mutation which reduces the function of the gene, wherein the gene has an  $\text{Err}\alpha$  binding site, a Gapba binding site, or both, wherein if a gene from the subject contains the mutation then the subject is at risk of developing the disorder.

48-77. (Canceled)

78. **(Withdrawn - Currently Amended)** A method of detecting statistically-significant differences in the expression level of at least one biomarker belonging to a biomarker set, between the members of a first and of a second experimental group, comprising:
- (a) obtaining a biomarker sample from members of the first and the second experimental groups;
  - (b) determining, for each biomarker sample, the expression levels of at least one biomarker belonging to the biomarker set and of at least one biomarker not belonging to the set;
  - (c) generating a rank order of each biomarker according to a difference metric of its expression level in the first experimental group compared to the second experimental group;
  - (d) calculating an experimental enrichment score for the biomarker set by applying a non-parametric ~~non-parametric~~ statistic; and
  - (e) comparing the experimental enrichment score with a distribution of randomized enrichment scores to calculate the fraction of randomized enrichment scores greater

than the experimental enrichment score, wherein a low fraction indicates a statistically-significant difference in the expression level of the biomarker set between the members of the first and of the second experimental group.

79-92. (Canceled)

93. **(Currently Amended)** A method of identifying an agent that regulates expression of OXPHOS-CR genes, the method comprising
- (a) contacting (i) an agent to be assessed for its ability to regulate expression of OXPHOS-CR genes with (ii) a test cell; and
  - (b) determining whether the expression of at least two OXPHOS-CR gene products show a coordinate ~~increase~~change in the test cell compared to an appropriate control, wherein a coordinate ~~increase~~change in the expression of the OXPHOS-CR gene products indicates that the agent regulates the expression of OXPHOS-CR genes.

94-105. (Canceled)

106. **(Currently Amended)** The method of claim 93, wherein a coordinate ~~increase~~change in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential ~~enhancer~~modulator of the expression or activity of  $\text{Err}\alpha$  or  $\text{G}\alpha\text{bp}$ .
107. **(Currently Amended)** The method of claim 106, wherein a coordinate ~~increase~~change in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential agent for ~~enhancing~~modulating mitochondrial biogenesis, expression of Nuclear Respiratory Factor 1 (NRF-1),  $\beta$ -oxidation of fatty acids, total mitochondrial respiration, uncoupled respiration, mitochondrial DNA replication, expression of mitochondrial enzymes, or skeletal muscle fiber-type switching.

108. **(Currently Amended)** The method of claim 93, wherein the agent to be assessed is a small molecule~~method comprises determining whether the expression of at least two OXPHOS-CR gene products show a coordinate increase in the test cell as compared to an appropriate control.~~
109. **(Currently Amended)** The method of claim 93 ~~108~~, wherein a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
110. **(Currently Amended)** The method of claim 93 ~~108~~, wherein a coordinate increase in the expression of the OXPHOS-CR gene products further indicates that the agent is a potential agent for increasing expression or activity of  $\text{Err}\alpha$  or  $\text{Gabp}$ .
111. **(Previously Presented)** The method of claim 110, wherein an agent that increases expression or activity of  $\text{Err}\alpha$  or  $\text{Gabp}$  is a potential agent for the treatment of a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
112. **(Currently Amended)** The method of claim 110, wherein the test cell is a mammalian cell~~a coordinate increase in the expression of the OXPHOS-CR gene products indicates that the agent is a potential agent for increasing mitochondrial biogenesis, expression of Nuclear Respiratory Factor 1 (NRF-1),  $\beta$  oxidation of fatty acids, total mitochondrial respiration, uncoupled respiration, mitochondrial DNA replication, expression of mitochondrial enzymes, or skeletal muscle fiber type switching.~~
113. **(Withdrawn)** The method of claim 93, further comprising assessing the effect of the agent on mitochondrial number or on a mitochondrial function.

- 114. **(Withdrawn)** The method of claim 93, further comprising assessing whether the agent increases a desired biological response that is impaired in subjects having a disorder that is characterized by glucose intolerance, insulin resistance, or decreased mitochondrial function.
- 115. **(Withdrawn - Currently Amended)** The method of claim 93, wherein step (a) is performed in vitro, and the method further comprises ~~comprising~~ administering the agent to a mammalian organism.
- 116. **(Withdrawn)** The method of claim 115, wherein the mammalian organism is human.
- 117. **(Withdrawn)** The method of claim 115, wherein the mammalian organism is a test animal that serves as a model for a disorder characterized by glucose intolerance, insulin resistance, or decreased mitochondrial function.
- 118. **(New)** The method of claim 93, wherein the test cell is a mammalian cell.
- 119. **(New)** The method of claim 118, wherein the test cell is a skeletal muscle cell.
- 120. **(New)** The method of claim 118, wherein the test cell is in an organism.
- 121. **(New)** The method of claim 118, wherein the agent to be assessed is a small molecule.
- 122. **(New)** The method of claim 93, wherein the method is performed in parallel on multiple populations of cells and each population is contacted with a different agent to be assessed.
- 123. **(New)** The method of claim 122, wherein the agents are members of a compound library.
- 124. **(New)** The method of claim 109, wherein the agent is useful for treating a human suffering from a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.

125. **(New)** The method of claim 111, wherein the agent is useful for treating a human suffering from a disorder that is characterized by glucose intolerance, insulin resistance or reduced mitochondrial function.
126. **(New)** The method of claim 93, further comprising determining whether the agent also regulates expression of genes that are not OXPHOS-CR genes.